Clinical aspects

Chapter 5

Hormonal contraceptive use after venous thrombosis: practice from 1999-2004

Bernardine H. Stegeman
Hetty Jolink
Frans M. Helmerhorst
Frits R. Rosendaal
Astrid van Hylckama Vlieg

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Abstract

Background: Current guidelines state that women using combined hormonal contraceptives at the time of a venous thrombosis event should stop using these combined preparations. Progestagen-only contraceptives are advised to be used in these women. The aim of this study is to determine to what extent the guidelines concerning hormonal contraceptive use after a venous thrombosis are followed in daily practice.
Methods: Women younger than 50 years who experienced a hormonal contraceptive-associated venous thrombosis were selected from a case-control study, the MEGA study. Data on hormonal contraceptive use after a venous thrombosis was available through an interview at venipuncture. In addition, participants from the follow-up study provided data on advice, given by a physician, to stop hormonal contraceptive use. Risk differences with 95% confidence interval (CI) were calculated.
Results: 703 women were included with a mean follow-up at interview of 10.8 months (range: 2.1 to 35.4 months). 521 (74%) women stopped hormonal contraceptive use, 63 (9%) changed to a different contraceptive method, and 119 (17%) continued the same method. 143 (21%) of 682 women who used a combined oral contraceptive at the thrombotic event were still using a combined preparation after the event contrasting the guidelines. Women who continued their contraceptive use had less often a positive family history of venous thrombosis and more often surgery (RD 19%, 95%CI: 9 to 30%) or a plaster cast (RD 17%, 95%CI: 3 to 34%) at the time of venous thrombosis than women who stopped. 39 (12%) of 332 women using a combined preparation and who received advice to stop from a physician, continued their combined oral contraceptive.
Conclusions: The finding that women continue their combined oral contraceptive use after receiving advice to stop is a real concern, in particular since there are indications that this use could increase the risk of a recurrence.

Introduction

Combined oral contraceptive use (containing ethinylestradiol and a progestagen) is associated with an increased risk of venous thrombosis. Regarding the use of combined oral contraceptives after a hormonal contraceptive-associated venous thrombosis, the WHO guideline from 2004 recommends that women with a history of venous thromboembolic disease should refrain from using combined hormonal contraceptives[1]. The same recommendation is stated in national guidelines from the Netherlands[2,3]. In addition, package insertions of combined oral contraceptives advise women to refrain from the use of these contraceptives in case of a (experienced) thromboembolic event. By law, the manufacturer is required to list contra-indications on package insertions in the Netherlands. Both national and WHO guidelines state that progestagen-only contraceptives such as progestagen-only pills or intra-uterine devices may be used in case of a history of venous thrombosis[1–3].

Little is known about hormonal contraceptive use after venous thrombosis in clinical practice. Only one study assessed whether continuing hormonal contraceptives influenced the risk of a recurrence. In the Leiden Thrombophilia Study (LETS) it was shown that almost 30% of women continued oral contraceptive use after an oral contraceptive-associated venous thrombosis[4] and after a mean follow-up of 7.3 years approximately 45% either continued or restarted oral contraceptives[5]. The recurrence rate in women who continued or restarted the use of a hormonal contraceptive was much higher (48.8 per 1000 patient-years) than in women who stopped hormonal contraceptive use (10.5 per 1000 patient-years) (age-adjusted incidence rate ratio 4.3, 95%CI: 1.7 to 11.1)[6].

There is limited knowledge regarding daily medical practice after a hormonal contraceptive-associated venous thrombotic event. To assess the adherence to the recommendations in the guidelines, short term follow-up data on hormonal contracep-

tive use was analyzed from the cases enrolled in the MEGA study (a case-control study of venous thrombosis). We focused in particular on what proportion of patients with a hormonal contraceptive-associated venous thrombosis stopped, changed or continued their hormonal contraceptive use. We determined what changes were made when women changed to a different hormonal contraceptive method after a thrombotic event. Secondly, we assessed whether acquired risk factors for venous thrombosis were associated with the decision to stop, change or continue oral contraceptive use. In a proportion of these women, long term follow-up data was available with information about the advice received from the physician. In these women, we assessed the proportion of women who did receive advice to stop their oral contraceptive use and how many followed this advice.

Methods

Study design For this study, we included patients with a first episode of deep venous thrombosis or a pulmonary embolism, who were enrolled in a large case-control study on risk factors for venous thrombosis, i.e., the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study[7]. Consecutive patients younger than 70 years with a first symptomatic deep vein thrombosis in the leg or arm or pulmonary embolism were recruited from six anticoagulation clinics in the Netherlands between 1 March 1999 and 31 August 2004 (N=5183). Control subjects were partners or recruited via random digit dialling. Only the case group is included in the current analysis.

All patients completed a detailed questionnaire on risk factors for venous thrombosis, including the use of oral contraceptives. The questions covered a period of one year before the thrombotic event. Three months after discontinuation of the anticoagulation therapy, patients were invited to the anticoagulation clinic for a blood sample. During this visit participants were interviewed

regarding the period from the venous thrombotic event until the venipuncture. This interview included items on the change of hormonal contraceptive methods since the diagnosis of venous thrombosis. Patients included in the MEGA case-control study subsequently took part in a follow-up study. In the follow-up questionnaire, a question was asked whether or not advice from the treating physician was received regarding contraceptive use after the first event. Because not all patients participated in this follow-up study, data was available in a proportion of the included women for the current analysis.

Of 5183 cases included in the MEGA study, 2799 were women of whom 1703 were younger than 50 years. Women not taking hormonal contraceptives at the time of a venous thrombosis were excluded (N=569). Of 431 women no data was available on hormonal contraceptive use after the thrombotic event, i.e., at the time of venipuncture. In total, 703 women were included in the current analysis of which 414 women also filled in the follow-up questionnaire and thus had data on advice received from a physician.

Analysis We first determined what proportion of women with venous thrombosis during hormonal contraceptive use stopped, continued, or changed their hormonal contraceptive use after the event. Baseline characteristics (i.e., age, body mass index (BMI), current smoking, positive family history, and type of contraception) were studied separately for women who stopped, changed, or continued their contraception. BMI was analyzed as a categorical variable with three categories: BMI $\leq$25 kg/m^2, BMI 25-30 kg/m^2, and BMI >30 kg/m^2. Smoking behaviour was represented as current, past, or never smokers. A positive family history was defined as having one or more first-degree relatives with a history of venous thrombosis. Contraception was divided into combined hormonal contraceptives (i.e., containing ethinylestradiol and a progestagen) and progestagen-only contraceptives. The most commonly used administration route for combined

formulations is orally but occasionally it is administered transdermally or transvaginally. Progestagen-only formulations are administered orally (mini pill) as well as subcutaneously (via implant or injection) or intrauterinely (intrauterine device). In our study, none of the women used a combined transdermal patch or combined vaginal ring. All other applications of hormones were used. Combined oral contraceptives were further subdivided according to the type of progestagen used; first generation (i.e., lynestrenol and norethisteron), second generation (i.e., levonorgestrel), and third generation combined oral contraceptives (i.e., gestodene, desogestrel and norgestimate). The progestagens introduced after the third generation progestagens, i.e., cyproterone acetate and drospirenone, were analysed separately. Progestagen-only contraceptives were subdivided into oral progestagen-only contraceptives (the so-called progestagen-only pills (POP)), hormonal intra-uterine device, implants, and injectables.

Secondly, we assessed which type of hormonal contraceptive women started to use when they changed their hormonal contraceptive use after the thrombotic event.

Thirdly, we determined whether exposure to an acquired risk factor for venous thrombosis was associated with stopping, changing, or continuing to use hormonal contraceptives. The following acquired risk factors were taken into account: surgery, plaster cast, immobilization, injury, and travel. A thrombotic event was classified as secondary to surgery, plaster cast, immobilization, or injury when one or more of these risk situations had occurred within 3 months prior to the thrombotic event. A thrombotic event was classified as secondary to travel when a patient had travelled for more than 4 hours in the period of eight weeks prior to the thrombotic event.

Finally, in women with data about advice received from a physician, we determined what proportion of women stopped, changed, or continued their contraceptive use when they were advised to stop.

Risk differences (RD) with 95% confidence intervals (CI) were calculated between different proportions. The Newcombe method 10 was used to calculate these risk differences as this method performed better with low sample sizes[8]. All statistical analyses were performed with STATA, version 12.0 (Statacorp LP, College Station, TX, USA).

Results

A total of 703 women with a hormonal contraceptive-associated venous thrombosis provided information on contraceptive use after the event. At an average of 10.8 months (range: 2.1 to 35.4 months) after venous thrombosis, 521 (74%) women had stopped the use of hormonal contraceptives, 63 (9%) changed to another hormonal contraceptive and 119 (17%) had continued with the same contraceptive.

General characteristics of the study population are presented in table 5.1 for women who stopped, changed or continued hormonal contraceptives. On average, women were about the same age (stop: 36 years (range 18 - 49), change: 34 years (range 20 - 48) and continue: 36 years (range 18 - 49)). The proportion of women stopping, changing or continuing their hormonal contraceptive did not markedly differ between BMI categories or smoking behaviour. Women with a positive family history of venous thrombosis were more likely to stop and less likely to change or continued their hormonal contraceptive than women without a positive family history. The vast majority was using a combined preparation at the time of venous thrombosis and the most commonly used progestagen was a second or third generation progestagen. Women using a combined oral contraceptive were more likely to stop and less likely to change or continue their contraceptive than women using a progestagen-only contraceptive. While no difference in age was observed, users of a first generation progestagen in their combined oral contraceptives were more likely to stop their contraceptive use and users

of cyproterone acetate and drospirenone were more likely to continue their contraceptive than users of other progestagens.

Table 5.1: Baseline chacteristics

Women who	**Stop N=521**	**Change N=63**	**Continue N=119**
Age, mean (range), years	36 (18-49)	34 (20-48)	36 (18-49)
BMI[a], kg/m^2			
>30 (%)	126 (76)	11 (7)	29 (17)
25-30 (%)	156 (75)	20 (10)	33 (16)
<25 (%)	210 (73)	29 (10)	50 (17)
Smoking[a]			
Current (%)	213 (76)	22 (8)	45 (16)
Past (%)	89 (77)	10 (9)	17 (15)
Never (%)	203 (71)	30 (11)	52 (18)
Positive family history[a]			
Yes (%)	115 (82)	7 (5)	18 (13)
No (%)	300 (72)	40 (10)	75 (18)
Contraception			
Combined oral contraceptives (%)	508 (75)	60 (9)	114 (17)
First generation (%)	32 (86)	1 (3)	4 (11)
Second generation (%)	212 (76)	13 (5)	53 (19)
Third generation (%)	213 (74)	37 (13)	38 (13)
Cyproterone acetate (%)	45 (64)	8 (11)	17 (24)
Drospirenone (%)	6 (67)	1 (11)	2 (22)
Progestagen-only contraceptives (%)	12 (60)	3 (15)	5 (25)
Oral progestagen-only[b](%)	0 (0)	1 (100)	0 (0)
Intra-uterine device (%)	0 (0)	0 (0)	1 (100)
Implanon (%)	1 (100)	0 (0)	0 (0)
Injectables (%)	11 (65)	2 (12)	4 (24)
Unknown (%)	1 (100)	0 (0)	0 (0)

[a] Data on BMI, smoking, and family history was available in 665, 682, and 556 women, respectively.
[b] User of lynestrenol, a progestagen belonging to the first generation

An overview of the contraceptive used at and after the event among women who changed their contraceptive is given in table 5.2. The majority of these women changed to either a second gen-

eration combined oral contraceptive (41%) or to an intra-uterine device (40%). 54% of third generation combined oral contraceptive users switched to a second generation contraceptives, whereas 54% of second generation combined oral contraceptive users changed to an intra-uterine device (Table 5.2).

Regarding adherence to the guidelines, of 682 women who were using a combined oral contraceptive at the venous thrombosis event, 508 (74%) women discontinued use of combined oral contraceptives. However, 143 (21%) either changed to another combined oral contraceptive or continued to use their combined preparation, while 31 (5%) women changed to progestagen-only preparations.

At the time of interview not all women had stopped anticoagulant therapy. Hormonal contraceptive use might be continued to prevent pregnancy during anticoagulant therapy. 64 (10%) women were using anticoagulant therapy at time of the interview. After excluding these women, the distribution of women who stopped, changed or continued their contraceptive did not change; 421 (76%) women stopped, 46 (8%) changed and 85 (15%) continued their contraceptive use.

Risk differences (RD) in acquired risk factors - surgery, plaster cast, immobilization, injury and travel - for the women who stopped, continued or changed their contraceptive method are presented in table 5.3. Of the 349 women not exposed to any risk factor, 267 (77%) stopped, 31 (9%) changed and 51 (15%) continued their contraceptive use. 337 women were exposed to one or more acquired risk factors, of which 240 (71%) stopped, 31 (9%) changed and 66 (20%) continued their contraceptive use. Women, who had undergone surgery within 3 months prior to the diagnosis of thrombosis, were less likely to stop their contraceptive use than unexposed women (58% versus 77%, RD -19%, 95%CI: -30 to -8%) and more likely to continue their contraceptive use (34% versus 15%, RD 19%, 95%CI: 9 to 30%). Women, who had a plaster cast within 3 months prior to the diagnosis of thrombosis, were less likely to stop their contraceptive use than

Table 5.2: Pattern of changes after an hormonal contraceptive-associated venous thrombosis event

	Contraceptive method after venous thrombosis							
Contraceptive at event	**1st gen**	**2nd gen**	**3rd gen**	**DRSP**	**POP**	**IUD**	**Implanon**	**Injectables**
Combined oral contraceptives								
1st gen (%)	-	-	-	-	-	1 (100)	-	-
2nd gen (%)	-	3 (23)	1 (8)	-	-	7 (54)	-	2 (15)
3rd gen (%)	-	20 (54)	-	-	2 (5)	10 (27)	2 (5)	3 (8)
CPA (%)	-	3 (38)	1(13)	1(13)	-	3 (38)	-	-
DRSP (%)	-	-	-	-	-	1 (100)	-	-
Progestagen-only contraceptives								
POP (%)	-	-	-	-	-	1 (100)	-	-
Injectables (%)	-	-	-	-	-	2 (100)	-	-
Total	0	26 (41)	2 (3)	1 (2)	2 (3)	25 (40)	2 (3)	5 (8)

1st gen, first generation progestagen; 2nd gen, second generation progestagen; 3rd gen, third generation progestagen; CPA, cyproterone acetate; DRSP, drospirenone; POP, progestagen-only pills; IUD, intra-uterine device

unexposed women (59% versus 77%, RD -17%, 95%CI: -35 to -1%) and more likely to continue their contraceptive use (31% versus 15%, RD 17%, 95%CI: 3 to 34%). Regarding women exposed to immobilization, injure or travel, no differences were observed between exposed and unexposed women.

Finally, a total of 414 women had information on whether they received advice to stop using hormonal contraceptives. 341 (82%) were advised to stop using hormonal contraceptives, while 67 (16%) women did not receive this advice. Six women stated that they did not know whether they received any advice. Women who received advice regarding hormonal contraceptive use were more likely to stop their contraceptive use than women who did not receive any advice (83% versus 34%, RD 49%, 95%CI: 36 to 60%) (Table 5.4). Of 332 women using a combined oral contraceptive who were advised to stop, 277 (83%) did stop their preparation, 16 (5%) changed to progestagen-only contraceptives and 39 (12%) either continued or changed to another combined preparation.

Discussion

In this study we found that the majority of women with a first episode of venous thrombosis while using a hormonal contraceptive method had discontinued the use of hormonal contraceptives after the thrombotic event. However, about 25% of these women either changed or continued their contraceptive. Anticoagulant therapy at the time of interview did not explain why women continued their contraceptive use. Women who had had a thrombosis following surgery or plaster cast continued their hormonal contraceptive method more often than unexposed women. The majority of the women who received advice to stop using their hormonal contraceptive, did follow this advice.

The majority of women changing oral contraceptives, change to a combined preparation with a second generation progestagen or an intra-uterine device. The reason behind changing to a

Table 5.3: Transient risk factors in women who stop, continue or change their hormonal contraceptive method

	Stop N=521	**RD (95%CI)**	**Change N=69**	**RD (95%CI)**	**Continue N=119**	**RD (95%CI)**
Risk factor						
None (%)	267 (77)	Reference	31 (9)	Reference	51 (15)	Reference
Any (%)	240 (71)	-5 (-12 to 1)	31 (9)	0 (-4 to 5)	66 (20)	5 (-1 to 11)
Surgery (%)	48 (58)	-19 (-30 to -8)	7 (8)	0 (-6 to 8)	28 (34)	19 (9 to 30)
Immobilization (%)	70 (70)	-7 (-17 to 3)	14 (14)	5 (-1 to 14)	16 (16)	1 (-6 to 11)
Plaster cast (%)	19 (59)	-17 (-35 to -1)	3 (9)	1 (-7 to 16)	10 (31)	17 (3 to 34)
Injury (%)	73 (74)	-3 (-13 to 6)	8 (8)	-1 (-6 to 7)	18 (18)	4 (-4 to 13)
Travel (%)	108 (82)	6 (-3 to 13)	8 (6)	-3 (-7 to 3)	15 (11)	-3 (-9 to 4)
Advice to stop						
Do not know	3 (50)		1 (17)		2 (33)	
No	23 (34)	Reference	9 (13)	Reference	35 (52)	Reference
Yes	284 (83)	49 (36 to 60)	27 (8)	-6 (-16 to 2)	30 (9)	-43 (-55 to -31)

second generation combined oral contraceptive may be the lower risk for venous thrombosis in these users compared with either third generation or cyproterone acetate users [9–12]. However, these risk estimates are for a first event and whether these estimates can also be applied to a second event is unclear.

The association between the presence of certain acquired risk factors (surgery or a plaster cast) and the continuation of oral contraceptive use suggests that physicians think it is safe to continue oral contraceptives when a strong acquired risk factor for thrombosis has been established as an (additional) cause of the thrombotic event. Venous thrombosis is a multicausal disease, i.e., for the occurrence of deep vein thrombosis a combination of risk factors needs to be present [13]. The recurrence rate in surgically provoked events is low in patients without other clinical risk factors [14,15], whether this is also the case in women with a surgically provoked thrombotic event who use and continue to use oral contraceptives is unknown. It is therefore unclear whether the continuation of combined oral contraceptives is justified in this subgroup of patients.

Little is known about hormonal contraceptive use after venous thrombosis in clinical practice and about the risk of a recurrence in hormonal contraceptive users. The recommendations in the WHO guideline are based on studies which only included first events. No data on second events were available before publication of the WHO guideline in 2004. Only one study, which was published in 2010, analyzed the recurrence rate of thromboembolic disease in women who had actually continued or stopped oral contraceptive use after their first episode of oral contraceptive-associated venous thrombosis. They found that an increased rate for venous thrombosis in hormonal contraceptive users compared to non-users [6]. However, only 11 recurrences were found among hormonal contraceptive users. The number became too low per type of contraceptive to infer any other conclusions.

The statements regarding progestagen-only contraceptive use in the WHO guideline were based on one observational study

from the WHO[16]. Because of different types of progestagen and different doses for different applications, it is difficult to come to a conclusion about progestagen-only preparations and the risk of a first event. Even less is known about progestagen-only preparations and the risk of a second event. The previous study also reported on recurrences in progestagen-only preparations[6]; however, only 2 recurrences were observed in injectable users among a few progestagen-only preparation users.

This is one of the few studies to provide information on contraceptive use after a hormonal contraceptive-associated venous thrombosis. We had detailed information on contraceptive use before and after venous thrombosis, as well as on acquired risk factors. Therefore we were able to examine whether the presence of these risk factors was associated with the decision to stop or continue oral contraceptives, although we do not know whether this was actually taken into account with the decision making. Although we know whether these women were advised to stop their contraceptive use, we do not know why women stopped, changed or continued their contraceptive use. In particular, in women who received advice to stop using their contraceptive, it would be beneficial to know their reason to continue their contraceptive. In the Netherlands, the WHO guideline is implemented in national guidelines and we observed that about 20% do not follow the advice from the physician to stop their contraceptive use. The percentage of women receiving no advice may be different per country depending on implementation of guidelines. However, the problem that women continue their combined oral contraceptive use after receiving advice to stop is a real concern.

In conclusion, the fact that women seemed to disregard the advice from a physician is a real concern, emphasized by the potential increased risk of a recurrence when continuing hormonal contraceptives.

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